

Application Ser. No.: 10/031,764
Filing Date: September 30, 2002
Examiner: Audet, Maury A.

Remarks

In the Office Action, the Examiner noted that claims 1-7, 9 and 10 are pending in the application; and that claims 1-7, 9 and 10 are rejected. By this amendment, claims 1 to 6, 9 and 10 have been amended. Thus, claims 1-7, 9 and 10 are pending in the application. No new subject matter has been inserted through these amendments. All of the amendments are fully supported by the specification.

More specifically, claims 1, 2 and 6 have been amended to overcome the outstanding rejections and are further discussed below. Claims 3, 4, 5, 9 and 10 have been amended to correct certain of the obvious errors. For instance, claims 3-5 have been amended to recite the claims with definitive article "The" as they depend directly upon claim 1 reciting further limitations. Claim 4 has also been amended to provide the missing phrase "the nitrogen atom of the secondary amine is part of" in option 3) of the limitation as recited therein. Similarly, claims 9 and 10 have been amended to correct certain of the obvious errors, e.g., in claim 9 there was a duplicate recitation of "C₂-C₁₂ alkyl," which has been deleted, whereas in claim 10 there was incorrect recitation of "C₁-C₁₂ alkenyl," which has been correctly amended to read as "C₂-C₁₂ alkenyl." Similarly, in claim 1, there was an incorrect recitation of "C₁-C₂₀ alkyl," which has been amended to read correctly as "C₉-C₂₀ alkyl." As noted, support for all of these amendments can be found at various places of the specification. The Examiner's rejections are respectfully traversed below.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-7, 9 and 10 stand rejected under 35 U.S.C. 102(b) as being anticipated by Balkovec et al. I (US 5,378,804; also cited within Applicant's PCT/EP00/06769 Form 409 as Document 4 (D4), under it's WO continuity WO-A-9421677).

In particular, the Examiner alleges that Balkovec et al. teach cyclohexapeptides of formula I (see abstract) and formula IV (see Example 1) with secondary amine selected from dimethyl amine (examples 26-27; col. 29, lines 12-15, 49-51) as antifungal compositions (abstract) and methods of making the same (Examples and entire

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disclosure). However, it is respectfully submitted that the Examiner is confused with the recitation of secondary amine as to its position in the present invention and the disclosure of Balkovec et al. I. The present invention recites a $-\text{CH}_2\text{-sec.amine}$ as a substituent at R_8 or R_9 , both of which are on the phenyl ring of the compound of formula I as recited in claim 1 of the present invention. In fact, Balkovec et al. teach compounds having no substituents on the phenyl ring other than $-\text{OH}$ at the 4-position. On the other hand, the alleged secondary amine in Balkovec I et al. compounds is at position R_1 (i.e., $-\text{NR}^{\text{II}}\text{R}^{\text{III}}$ of Balkovec et al.). However, claims 1-7, and 9-10, as amended, do not recite R_1 as being secondary amine or a derivative thereof. As stated by a court:

Anticipation is established if *every element of a properly construed claim* is present in a single prior art reference¹ (emphasis added).

Thus, it is respectfully submitted that claims 1-7 and 9-10 are not anticipated by Balkovec et al. I. Accordingly, it is respectfully submitted that claims 1-7 and 9-10 fully satisfy the requirements of 35 U.S.C. § 102(b), and therefore, withdrawal of rejection as to claims 1-7 and 9-10 is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-4, 6-7, and 9-10 stand rejected under 35 U.S.C. 102(b) as being anticipated by Balkovec et al. II (US 5,541,160; also cited within Applicant's PCT/EP00/06769 Form 409 as Document 1 (D1), under it's WO continuity WO-A-9527074).

Specifically, it is alleged that Balkovec et al. II teach cyclohexapeptides of formula I (see abstract) and formula IV (see col. 4, SEQ ID NO:3) as antifungal compositions (col. 1, 1st para) and methods of making the same (Examples, entire disclosure).

However, it is again submitted that the compounds of the present invention as particularly recited in amended claims 1-4, 6-7 and 9-10 are not anticipated by Balkovec

¹ See *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.* 45 F.3d 1550, 1554 (33 USPQ2d 1496) (Fed. Cir. 1995).

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et al. II. In particular, the substituent R_1 of the compound of formula I or formula IV (which is equivalent in position to substituent R_3 of compound of formula I of Balkovec et al. II) of the present invention do not include any of the substituents $-H$, $-OH$, $-O(CH_2)_nNR^VR^V$, or $-O(CH_2)_nNR^VR^VR^{VII}Y$. On the other hand, instant amended claims 1-4, 6-7 and 9-10, recite uniquely different substituent R_1 of the compound of formula I or formula IV. Thus, it is respectfully submitted that claims 1-4, 6-7 and 9-10 are not anticipated by Balkovec et al. II. Accordingly, it is respectfully submitted that claims 1-4, 6-7 and 9-10 fully satisfy the requirements of 35 U.S.C. § 102(b), and therefore, withdrawal of rejection as to claims 1-4, 6-7 and 9-10 is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-7, 9 and 10 stand rejected under 35 U.S.C. 102(b) as being unpatentable over Balkovec et al. II (US 5,541,160; also cited within Applicant's PCT/EP00/06769 Form 409 as Document 1 (D1), under it's WO continuity WO-A-9527074) in view of Balkovec et al. I (US 5,378,804; also cited within Applicant's PCT/EP00/06769 Form 409 as Document 4 (D4), under it's WO continuity WO-A-9421677).

Specifically, the Examiner admits that "Balkovec et al. II do not expressly teach a compound with a secondary amine of i.e. dimethylamine (Applicant's claim 5)" as substituent R_8 (or R_9) on the tyrosine phenyl ring. Nevertheless, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a secondary amine such as dimethylamine in the compounds of Balkovec et al. II, since Balkovec et al. I teach the advantageous use of secondary amines such as dimethylamine in the same family of cyclohexapeptides of Balkovec et al. II."

However, it is respectfully submitted that the Examiner is confused as to the recitation of secondary amine in the present invention and Applicants further submit that the Examiner has not provided a motivation to combine references. Thus, it is submitted that claims 1-7, 9 and 10, as amended, are patentably distinguishable from the teachings

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of Balkovec et al. II in view of Balkovec et al. I, and therefore, withdrawal of this rejection is respectfully requested.

First, as we discussed above, the recitation of secondary amine appears only within the definition of R_8 or R_9 where it is recited as $-\text{CH}_2\text{-sec-amine}$. As noted, the substituents R_8 and R_9 are at the either side of the ortho position of the hydroxyl group on the tyrosine phenyl group of formula I or IV as respectively recited in claims 1 and 10. Various preferred embodiments of secondary amines are further recited in claim 5 including dimethylamine. As admitted by the Examiner, Balkovec et al. II do not teach the use of any of the secondary amines especially as $-\text{CH}_2\text{-sec-amine}$ including dimethyl amine. Furthermore, Balkovec et al. I do not teach any of the substituents at R_8 (or R_9) position. Naturally, contrary to the views of the Examiner, Balkovec et al. II alone or in view of Balkovec et al. I do not teach or suggest the use of $-\text{CH}_2\text{-sec-amine}$ as a substituent at either R_8 or R_9 position. Furthermore, neither Balkovec et al. II nor Balkovec et al. I provide any structure activity relationship so as to provide sufficient impetus to one of skill in the art of medicinal chemistry to arrive at the present invention.

On the other hand, the compounds of the present invention provide uniquely three specificities none of which are taught or suggested by Balkovec et al. II or Balkovec et al. I. First, as we discussed above, the R_1 group at the 5-ornithine position of compound of formula I of the present invention is much different from those of Balkovec et al. II or Balkovec et al. I. Second, the R_3 group at the homotyrosine-4 of the present invention is also much different from those recited in Balkovec et al. II or Balkovec et al. I (the only overlapping R_3 group with Balkovec I or II and the present invention is $-\text{OH}$). Finally, as we argued above, the R_8 and R_9 at the ortho position of the phenolic hydroxyl of the homotyrosine unit of the present invention are much different from that disclosed in Balkovec et al. II or I.

More specifically, as we noted already above, Balkovec et al. I disclose compounds wherein the tyrosine unit is not substituted on the phenol ring (i.e., R_8 and R_9 are both hydrogen), but have amino substituent in the 5-ornithine (i.e., R_1 is $-\text{NR}^{\text{II}}\text{R}^{\text{III}}$). Similarly, Balkovec et al. II disclose compounds wherein the substituent in the 5-

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ornithine, R_1 having $-H$, $-OH$, $-O(CH_2)_nNR^V R^{VI}$, or $-O(CH_2)_nNR^V R^{VI} R^{VII+} Y^-$, all of which are different substituents from those taught by the present invention. Thus, it is submitted that it is not obvious to modify the compounds of Balkovec et al. II in view of Balkovec et al. I to arrive at the present invention at the time the Applicants made the instant invention. As stated by a court:

"Although suggestion to combine prior art references to achieve invention claimed in patent may be found in explicit or implicit teachings in references themselves, from ordinary knowledge of those skilled in art, or from nature of problem to be solved, there must still be evidence that skilled artisan, confronted with same problems as inventor and with no knowledge of claimed invention, would select elements from cited prior art references for combination in manner claimed; implicit, generalized finding that person of ordinary skill in art, faced with same problem as inventor, would have found claimed combination obvious is insufficient² (emphasis added).

In fact, it is submitted that in the present situation there is no suggestion to combine references as discussed in detail above. That is, each of Balkovec et al. I or II do not teach or even remotely suggest the compounds of the present invention. Even more importantly, the combination of Balkovec et al. I and II do not disclose how to obtain new compounds of the instant invention having the antifungal activities. In view of the foregoing, it is respectfully submitted that claims 1-7, 9 and 10, as amended, are patentably distinguishable from Balkovec et al. II in view of Balkovec et al. I, and therefore, fully satisfy the requirements of 35 U.S.C. § 103(a). Thus, withdrawal of rejection as to claims 1-7, 9 and 10 is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-7, 9 and 10 stand rejected under 35 U.S.C. 102(b) as being unpatentable over either Balkovec et al. I (US 5,378,804; also cited within Applicant's PCT/EP00/06769 Form 409 as Document 4 (D4), under it's WO continuity WO-A-

² *Ecolchem Inc. v. Southern California Edison*, 56 USPQ2d 1065 (Fed. Cir. 2000).

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9421677) or Balkovec et al. II (US 5,541,160; also cited within Applicant's PCT/EP00/06769 Form 409 as Document 1 (D1), under it's WO continuity WO-A-9527074).

In particular, the Examiner further alleges that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use varying amounts of starting materials and/or steps to arrive at the variations in the cyclohexapeptides of Balkovec et al. I or II, since both references advantageously teach the same family of compounds with modifications and because arrival at such modifications is matter of judicious selection by one of skill in the art and a matter of routine optimization thereto, absent evidence to the contrary." The Examiner further alleges that "from the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary."

However, it is respectfully submitted that the Examiner has erred in his obviousness analyses to arrive at the prima facie obviousness in this case. As we already argued above, there are clearly many distinguishing features of the present invention all of which are not taught or even remotely suggested by taking Balkovec et al. II alone or in combination with Balkovec et al. I so as to motivate one of ordinary skill in the art. On the other hand, in an obviousness analysis the Patent Office must identify where the prior art provides a motivating suggestion to make the modifications made by the instant invention, *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992). The mere fact that the prior art may be modified as suggested by an Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification, *In re Fritch*, 922 F.2d 1260, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992).

Clearly, properly applying the obviousness analysis requires a rigorous examination and analysis of the prior art. It also requires an understanding of the underlying principle of this analysis. Obviousness analysis was intended to leave behind

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discredited tests of patentability like "inventive leap", "flash of genius", etc. and instead simply base the decision to award a patent on whether the compound or method claimed is (1) sufficiently different from and (2) not suggested by the prior art. Whether the claimed invention is better than the prior art as evidenced or not by a "showing of criticality" simply has no place in the inquiry surrounding the establishment of a *prima facie* case of obviousness, unless the sole difference between the invention and the prior art is a numerical range.

In an obviousness analysis, the Board of Patent Appeals and Interferences ("Board") as well as the Court of Appeals for the Federal Circuit (CAFC) have provided guidance to determine whether or not the invention under examination is rendered obvious in view of the cited art. First, there must be logical reasoning which provides sufficient impetus for one of ordinary skill in the art to arrive at the claimed invention based on the prior art at the time the invention was made. As stated by the Board:

"..... fact that invention's theoretical mechanism can be reconstructed and explained by means of logic and sound scientific reasoning does not, however, support obviousness determination *unless that logic and reasoning would supply sufficient impetus to have led one of ordinary skill in art to combine references to make claimed invention*, and thus examiner cannot establish obviousness by locating references which describe various aspects of applicant's invention unless examiner also provides evidence of motivating force which would impel person skilled in art to do what applicant has done³. (emphasis added)

Applying these criteria to the present situation, it is respectfully submitted that the Examiner has not provided any evidence of motivating force such that a person skilled in the art would have done what Applicants have taught in the instant invention. That is, Applicants have specifically disclosed and claim discrete compounds of formula I as recited in claims 1-7, 9 and 10. As we discussed extensively above, Balkovec et al. I and II teach distinctively different compounds from the ones disclosed in the instant invention. Thus, we submit that there is no logic or sound scientific reasoning such that

³ *Ex parte Levengood* (Bd. Pat. App. & Int.) 28 USPQ2d 1300 (1993)

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one of ordinary skill in the art would combine these two references to arrive at the instant invention.

Second, as improperly alleged by the Examiner the courts have also looked for reasonable expectation of success in arriving at the claimed invention based on the cited prior art. As noted by the Federal Circuit:

"Rejection of claimed subject matter as obvious under 35 USC 103 in view of combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that such person would have reasonable expectation of success; *both suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure*⁴". (emphasis added)

Again, from the foregoing description of the cited prior art, neither one of the prior art suggests with any degree of certainty success in arriving at the present invention. In fact, as we argued above, the cited art does not even remotely suggest the present invention. Thus, in view of all of the arguments advanced above, it is respectfully submitted that claims 1-7, 9 and 10, as amended, are patentably distinguishable from Balkovec et al. I or Balkovec et al. II, and therefore, fully satisfy the requirements of 35 U.S.C. § 103(a). Thus, withdrawal of rejection as to claims 1-7, 9 and 10 is respectfully requested.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 1-7, 9 and 10 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

As noted above, Applicants concurrently submit herewith a petition for one-month extension of time to make this response timely. Applicants request the

⁴ *In re Vaeck* (CA FC) 20 USPQ2d 1438 (1991)

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Commissioner to charge these fees to Deposit Account No. 18-1982 for Aventis Pharmaceuticals Inc. Bridgewater, NJ. Please credit any overpayment to Deposit Account No. 18-1982.

August 1, 2005

Respectfully submitted,

Balaram Gupta

Balaram Gupta, Ph. D., J. D.

Registration No. 40,009
Attorney for Applicants

Aventis Pharmaceuticals Inc.
Patent Department
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626